Appendix A

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Statistical methods for sensitivity analyses: We conducted sensitivity analyses to assess the robustness of findings to unmeasured confounding using E-value methodology developed for observational research.[37] We calculated the minimum strength of an unmeasured confounder on the risk ratio scale (E-value), above and beyond the observed covariates, that would fully explain away the observed associations between buprenorphine discontinuation and each outcome, rendering the results non-significant (Exhibit A5).[37] For the five main outcomes, E-values were calculated using the odds ratios and 95% confidence intervals for the difference-in-differences estimates from fully adjusted models (Exhibit A7). For the rate of opioid use among users, the E-value was calculated using the risk ratio and 95% confidence interval for the difference-in-differences from the fully adjusted model (Exhibit A8).

Sensitivity analyses resulted in relatively large risk ratios (Exhibit A5) for inpatient services (E-value=2.6), emergency services (E-value=1.8), opioid-related hospital services (E-value=4.0), overdose events (E-value=2.9), prescription opioids (E-value=5.0), and the rate of prescription opioid use (E-value=5.4). E-values are similar to p-values in that they are continuous measures to assess the strength of the evidence for a given effect. However, unlike p-values, E-values have no predefined threshold.[37] Rather, the strength of the evidence is assessed in the context of the study design and results.

For example, continuous treatment was associated with significantly lower rates of prescription opioid use (IRR=0.3; Exhibit A8). According to the language suggested by developers of the E-value methodology, the observed rate ratio of 0.3 could only be explained away by an unmeasured confounder that was associated with both buprenorphine discontinuation and the rate of prescription opioid use by a risk ratio of 5.4-fold each, above and beyond the measured confounders, but weaker confounding could not do so. Because all E-values are substantially larger than the strength of the associations observed for all other known risk factors that were controlled for in the main analyses (Exhibits A7 and A8), it is unlikely that an unmeasured confounder has associations this large with both buprenorphine discontinuation and the outcomes.

Exhibit A1 Study design and sample definition

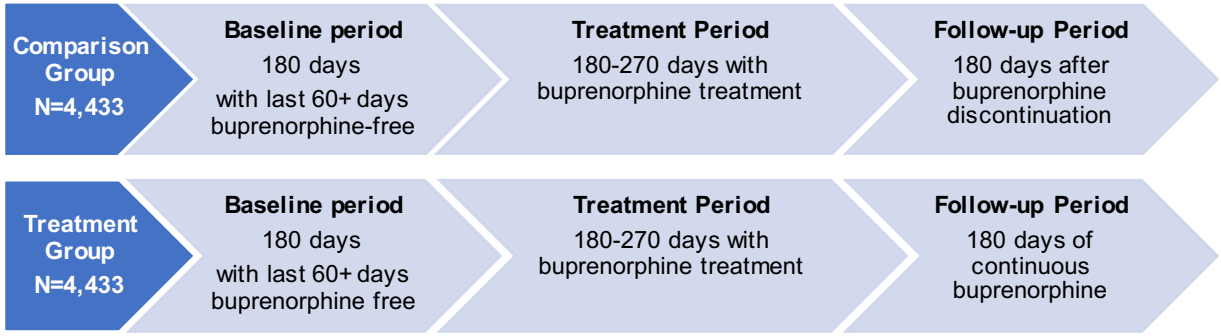
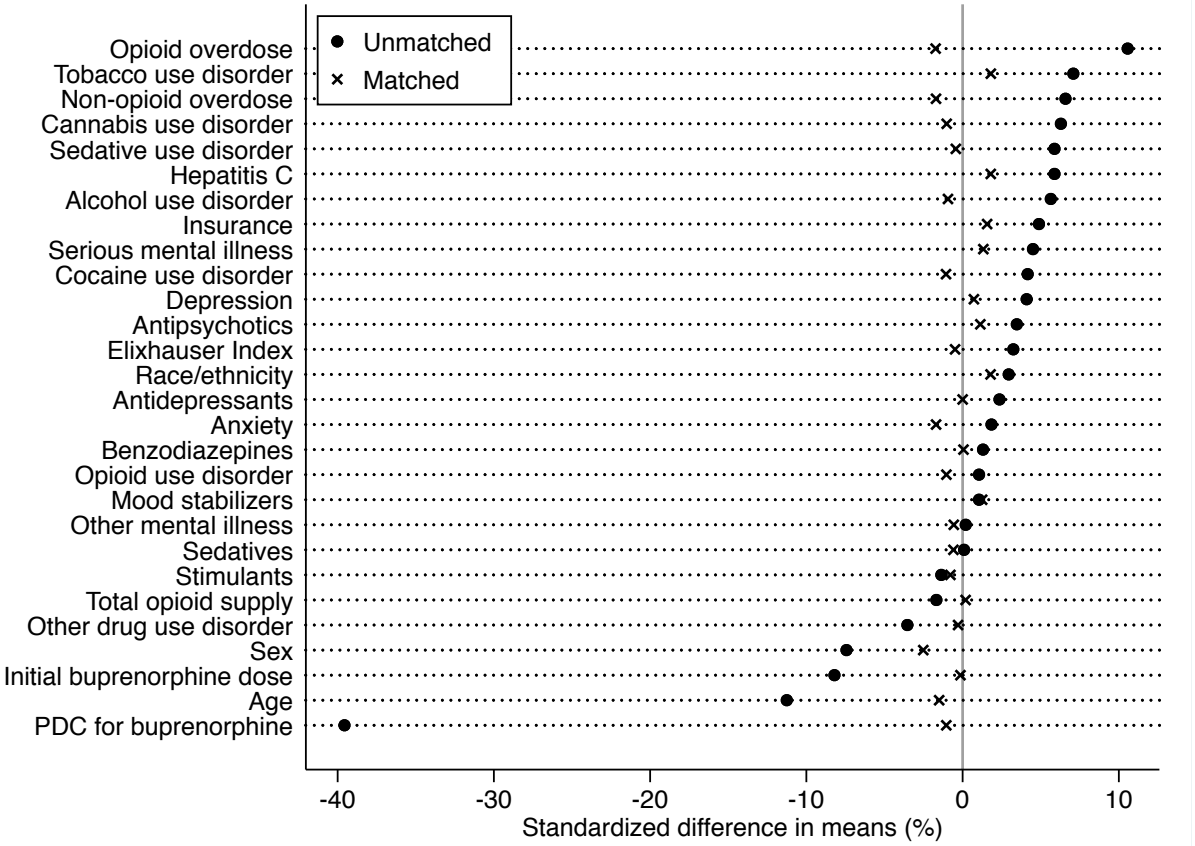
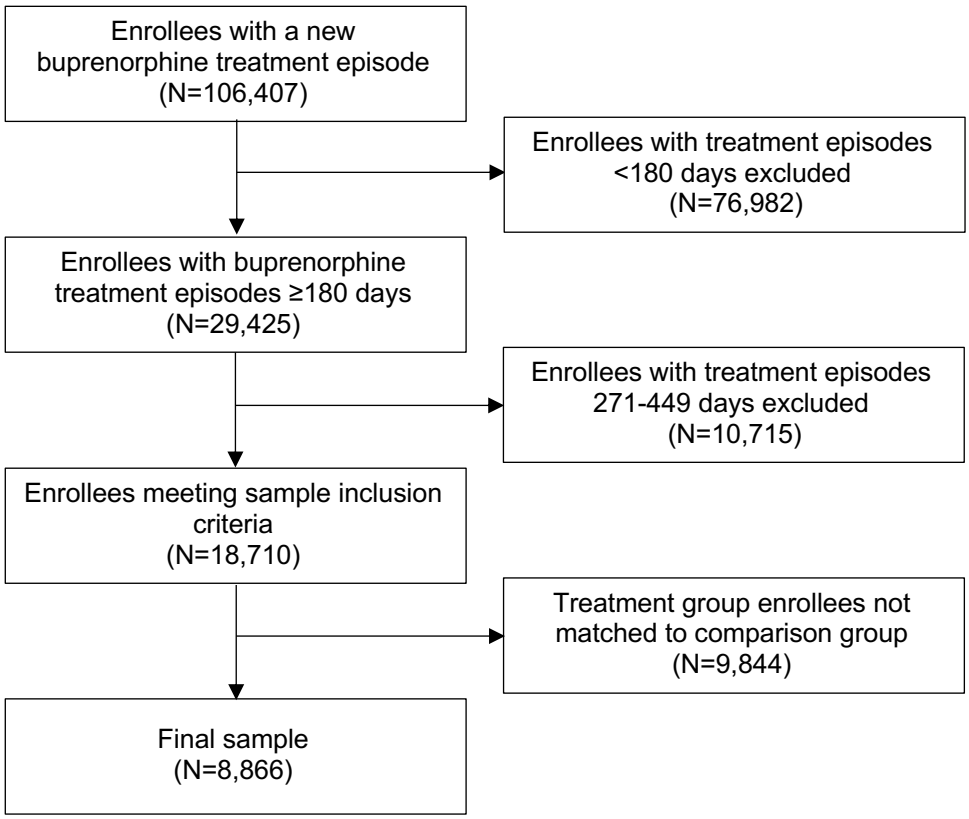


Exhibit A2 Balance between covariates before and after propensity score matching



SOURCE Authors' analysis of data from the MarketScan Multi-State Medicaid database, 2013-2017.
NOTES The standardized difference in means in an established measure of balance between groups. The standardized difference in means is calculated as the difference in the mean covariate value for each group divided by the standard deviation for the group that discontinued buprenorphine treatment. The standardized difference in means is calculated before and after propensity score matching to show the reduction in bias achieved by matching. The figure shows that propensity score matching reduced bias for nearly all covariates and that all covariates had a standard difference in means <20%, which is the cutoff for sufficiently balanced groups.

Exhibit A3 Sample selection criteria and sample size



SOURCE Authors' analysis of data from the MarketScan Multi-State Medicaid database, 2013-2017.

Exhibit A4 Analysis of parallel trends in the treatment period, comparing adults with continuous buprenorphine use to those who discontinued buprenorphine

Outcome	OR (95% CI)	p-value
All-cause inpatient use	1.0 (0.9, 1.0)	.09
All-cause emergency use	1.0 (1.0, 1.0)	.29
Opioid-related hospital use	0.9 (0.9, 1.0)	.08
All overdose events	0.9 (0.8, 1.0)	.26
Any prescription opioids	1.0 (0.9, 1.0)	.06
	IRR (95% CI)	**p-value**
Rate of prescription opioid use among users	1.0 (0.9, 1.0)	.31

SOURCE Authors' analysis of data from the MarketScan Multi-State Medicaid database, 2013-2017.
NOTES The test of parallel trends in the treatment period reports on a coefficient representing the interaction between study group (discontinued vs. continued treatment) and 30-day treatment periods prior to follow-up. All models included fixed effects for study group and study period and controlled for baseline sociodemographics (sex, age, race/ethnicity, insurance); comorbid medical (modified Elixhauser Index, hepatitis C), mental health (depression, anxiety, schizophrenia or bipolar disorder, other mental illness), and substance use diagnoses (opioids, alcohol, cannabis, tobacco, cocaine, sedatives, other drugs); health services (opioid overdose, non-opioid drug overdose, number of days with prescription opioid supply, and any use of prescription antidepressants, antipsychotics, stimulants, mood stabilizers, sedatives, or benzodiazepines); and buprenorphine treatment characteristics (initial dose, proportion of days covered).

Exhibit A5 Results of sensitivity analyses for unmeasured confounding of difference-in-differences results

Outcome	E-Value for the estimate	E-Value for the 95% CI
All-cause inpatient use	2.6	2.0
All-cause emergency use	1.8	1.6
Opioid-related hospital use	4.0	3.0
All overdose events	2.9	1.7
Any prescription opioids	5.0	4.3
Rate of use among users	5.4	4.0

SOURCE Authors' analysis of data from the MarketScan Multi-State Medicaid database, 2013-2017.
NOTES The E-Value represents the minimum strength, on the risk ratio scale, of the relationship of an unmeasured confounder with both buprenorphine discontinuation and the outcome, above and beyond the observed covariates, that would be required to render the results non-significant. The E-Value is calculated using the odds ratios and risk ratios and 95% confidence intervals from fully adjusted models for the effect of buprenorphine discontinuation on each outcome.

Exhibit A6 Person-month level changes in health care outcomes associated with buprenorphine discontinuation

Outcome	Discontinued Treatment, Unadjusted %			Continued Treatment, Unadjusted %			Difference-in-Differences, Adjusted percentage points
	Treatment Period	Follow-up Period	Change	Treatment Period	Follow-up Period	Change	
All-cause inpatient use	2.2	2.8	+0.6	1.8	1.5	-0.3	-0.9
All-cause emergency use	11.2	13.5	+2.3	9.3	9.3	-0.0	-2.4
Opioid-related hospital use	1.3	2.4	+1.0	1.0	0.8	-0.2	-1.2
All overdose events	0.5	1.0	+0.5	0.3	0.3	+0.1	-0.5
Any prescription opioids	4.5	7.9	+3.4	3.8	2.5	-1.3	-4.6
Rate of use among users	2.9	5.8	+2.9	2.6	1.3	-1.3	-3.6

SOURCE Authors' analysis of data from the MarketScan Multi-State Medicaid database, 2013-2017.
NOTES Analyses were conducted at the person-month level, defined as 30-day periods during treatment and follow-up. For the five main outcomes, unadjusted percentages were calculated among the full sample (n=8,866 persons) as any observed outcome per person in each 30-day period and summarized for each study group over 34,907 person-months of treatment and 26,598 person-months of follow-up to reflect the level of analysis. For the rate of prescription opioid use, unadjusted percentages were calculated among the subsample with any prescription opioid use during the study period and their matched pairs (n=4,494 persons) as the number of days with opioid supply per person in each 30-day period and summarized for each study group over 17,699 person-months of treatment and 13,482 person-months of follow-up. Adjusted difference-in-differences estimates were derived from GEE models controlling for baseline sociodemographics (sex, age, race/ethnicity, insurance); comorbid medical (modified Elixhauser Index, hepatitis C), mental health (depression, anxiety, schizophrenia or bipolar disorder, other mental illness), and substance use diagnoses (opioids, alcohol, cannabis, tobacco, cocaine, sedatives, other drugs); health services (opioid overdose, non-opioid drug overdose, number of days with prescription opioid supply, and any use of prescription antidepressants, antipsychotics, stimulants, mood stabilizers, sedatives, or benzodiazepines); and buprenorphine treatment characteristics (initial dose, proportion of days covered). The full models are provided in Appendix Exhibits A7 and A8. All adjusted difference-in-differences estimates are significant (p<0.001).

Exhibit A7 Fully adjusted logistic regression results for the five main health care outcomes (n=8,866)

	Outcome, OR (95% CI)				
	All-cause inpatient use	**All-cause emergency use**	**Opioid-related hospital use**	**All overdose events**	**Any prescription opioids**
Difference-in-differences					
Study group x Study period	0.6 (0.5, 0.7)	0.8 (0.7, 0.9)	0.4 (0.4, 0.6)	0.6 (0.4, 0.8)	0.4 (0.3, 0.4)
Sociodemographics					
Sex					
Male	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]
Female	1.4 (1.3, 1.6)	1.1 (1.0, 1.1)	0.9 (0.8, 1.1)	0.6 (0.5, 0.7)	1.2 (1.1, 1.3)
Age	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)
Race/ethnicity					
White	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]
Black	1.2 (1.0, 1.5)	1.3 (1.1, 1.4)	1.4 (1.1, 1.7)	1.4 (1.0, 2.0)	1.3 (1.1, 1.6)
Hispanic	1.1 (0.8, 1.7)	1.1 (0.9, 1.4)	1.9 (1.3, 2.9)	2.0 (1.1, 3.8)	1.0 (0.7, 1.5)
Other	0.8 (0.6, 1.1)	1.0 (0.9, 1.1)	0.9 (0.7, 1.3)	0.8 (0.5, 1.4)	1.0 (0.8, 1.3)
Insurance					
Fee-for-service	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]
Capitation	0.9 (0.8, 1.0)	1.0 (1.0, 1.1)	1.1 (0.9, 1.2)	0.9 (0.7, 1.0)	0.7 (0.6, 0.8)
Clinical Characteristics					
Mental Health Diagnoses					
Depression	1.3 (1.2, 1.5)	1.1 (1.0, 1.2)	1.2 (1.1, 1.4)	1.2 (1.0, 1.5)	1.1 (1.0, 1.2)
Anxiety	1.0 (0.9, 1.1)	1.1 (1.1, 1.2)	0.9 (0.8, 1.0)	0.9 (0.8, 1.1)	1.1 (1.0, 1.2)
Schizophrenia/Bipolar disorder	1.2 (1.0, 1.4)	1.3 (1.2, 1.4)	1.1 (0.9, 1.2)	1.4 (1.1, 1.8)	1.2 (1.1, 1.4)
Other	1.0 (0.8, 1.3)	1.0 (0.9, 1.1)	0.8 (0.6, 1.0)	0.8 (0.5, 1.3)	1.1 (1.0, 1.4)
Substance Use Disorders					
Opioids	1.1 (1.0, 1.2)	1.0 (1.0, 1.1)	1.5 (1.3, 1.7)	1.1 (0.9, 1.4)	0.9 (0.8, 0.9)
Alcohol	1.3 (1.1, 1.5)	1.1 (1.0, 1.2)	1.4 (1.2, 1.7)	1.1 (0.9, 1.5)	0.9 (0.8, 1.1)
Cannabis	1.3 (1.1, 1.5)	1.1 (1.0, 1.1)	1.3 (1.1, 1.6)	1.3 (0.9, 1.7)	1.0 (0.8, 1.1)
Tobacco	1.3 (1.2, 1.4)	1.4 (1.4, 1.5)	1.3 (1.2, 1.5)	1.0 (0.9, 1.3)	1.2 (1.1, 1.3)
Cocaine	1.7 (1.4, 2.0)	1.4 (1.3, 1.5)	1.5 (1.3, 1.9)	1.0 (0.7, 1.4)	1.3 (1.1, 1.6)
Sedatives	1.3 (1.1, 1.6)	1.1 (1.0, 1.3)	1.3 (1.0, 1.7)	1.0 (0.7, 1.6)	1.0 (0.8, 1.2)
Other	1.3 (1.2, 1.5)	1.2 (1.1, 1.3)	1.5 (1.3, 1.7)	1.1 (0.8, 1.4)	1.1 (1.0, 1.2)
Medical Comorbidities					
Elixhauser Index	1.0 (1.0, 1.1)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)
Hepatitis C	1.6 (1.5, 1.8)	1.3 (1.2, 1.3)	1.4 (1.2, 1.6)	1.8 (1.5, 2.3)	1.2 (1.0, 1.3)
Overdose events					
Opioid overdose	1.2 (1.0, 1.5)	1.1 (1.0, 1.2)	1.6 (1.3, 2.1)	1.7 (1.2, 2.4)	0.8 (0.7, 1.1)
Non-opioid drug overdose	1.1 (0.9, 1.4)	1.2 (1.0, 1.3)	1.2 (0.9, 1.5)	1.5 (1.1, 2.1)	0.9 (0.8, 1.1)
Prescription Drugs					
Antidepressants	1.0 (0.9, 1.1)	1.0 (0.9, 1.0)	1.0 (0.9, 1.1)	0.9 (0.7, 1.1)	1.1 (1.0, 1.2)
Antipsychotics	1.0 (0.9, 1.2)	1.1 (1.0, 1.1)	1.2 (1.0, 1.4)	1.3 (1.1, 1.7)	0.9 (0.8, 1.0)
Stimulants	0.9 (0.8, 1.1)	0.9 (0.8, 1.0)	0.9 (0.7, 1.1)	0.9 (0.6, 1.3)	1.2 (1.0, 1.3)
Mood stabilizers	1.1 (1.0, 1.2)	1.3 (1.2, 1.3)	1.3 (1.2, 1.5)	1.7 (1.4, 2.1)	1.1 (1.0, 1.2)
Benzodiazepines	1.1 (1.0, 1.2)	1.1 (1.1, 1.2)	1.2 (1.0, 1.3)	1.3 (1.0, 1.6)	1.1 (1.0, 1.2)
Sedatives	1.0 (0.8, 1.2)	1.1 (1.0, 1.2)	0.9 (0.7, 1.1)	1.1 (0.7, 1.5)	1.2 (1.0, 1.4)
Total opioid supply	1.0 (0.9, 1.1)	1.0 (0.9, 1.0)	1.0 (0.9, 1.1)	0.9 (0.7, 1.1)	1.1 (1.0, 1.2)
Buprenorphine Treatment					
Initial dose	0.9 (0.9, 1.0)	1.0 (1.0, 1.0)	0.9 (0.9, 1.0)	1.0 (0.9, 1.0)	1.0 (1.0, 1.0)
Proportion of days covered	0.0 (0.0, 0.1)	0.2 (0.1, 0.2)	0.0 (0.0, 0.1)	0.0 (0.0, 0.1)	0.3 (0.1, 0.5)

SOURCE Authors' analysis of data from the MarketScan Multi-State Medicaid database, 2013-2017.
NOTES Analyses were conducted at the person-month level, defined as 30-day periods during treatment and follow-up

Exhibit A8 Fully adjusted Poisson regression results for the rate of prescription opioid use among adults with any prescription opioid use during the study period and their matched pairs (n=4,494)

	Prescription opioid use among users, IRR (95% CI)
Difference-in-differences	
Study group x Study period	0.3 (0.3, 0.4)
Sociodemographics	
Sex	
Male	[Reference]
Female	1.0 (0.8, 1.1)
Age	1.0 (1.0, 1.0)
Race/ethnicity	
White	[Reference]
Black	1.1 (0.8, 1.6)
Hispanic	1.1 (0.5, 2.4)
Other	0.8 (0.5, 1.2)
Insurance	
Fee-for-service	[Reference]
Capitation	0.7 (0.6, 0.9)
Clinical Characteristics	
Mental Health Diagnoses	
Depression	1.2 (1.0, 1.5)
Anxiety	1.0 (0.8, 1.2)
Schizophrenia/Bipolar disorder	1.2 (0.9, 1.5)
Other	1.4 (1.0, 2.0)
Substance Use Disorders	
Opioids	0.9 (0.7, 1.0)
Alcohol	0.8 (0.6, 1.1)
Cannabis	1.0 (0.7, 1.3)
Tobacco	0.9 (0.8, 1.1)
Cocaine	1.0 (0.7, 1.5)
Sedatives	1.1 (0.7, 1.6)
Other	1.1 (0.8, 1.4)
Medical Comorbidities	
Elixhauser Index	1.0 (1.0, 1.0)
Hepatitis C	1.0 (0.8, 1.3)
Overdose events	
Opioid overdose	0.9 (0.6, 1.5)
Non-opioid drug overdose	0.7 (0.5, 1.0)
Prescription Drugs	
Antidepressants	1.1 (0.9, 1.3)
Antipsychotics	1.0 (0.8, 1.2)
Stimulants	1.3 (1.0, 1.7)
Mood stabilizers	1.2 (1.0, 1.4)
Benzodiazepines	1.0 (0.9, 1.2)
Sedatives	1.1 (0.9, 1.5)
Total opioid supply	1.1 (0.9, 1.3)
Buprenorphine Treatment	
Initial dose	1.0 (1.0, 1.0)
Proportion of days covered	1.0 (0.9, 1.0)

SOURCE Authors' analysis of data from the MarketScan Multi-State Medicaid database, 2013-2017.
NOTES Analyses were conducted at the person-month level, defined as 30-day periods during treatment and follow-up